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The PCB imbroglio

Airing the health effects of polychlorinated biphenyls is a good place to begin unraveling the confusion

Polychlorinated biphenyls (PCBs) are a family of 209 chlorinated aromatic hydrocarbons. About 100 of these PCBs are used commercially. The public now knows that PCBs are persistent in the environment and is concerned that they may have harmful health effects. These chemicals can accumulate in the food chain; this accumulation is related to their relative insolubility in water and their high solubility in lipids, such as body fats. Called bioconcentration, this action causes tissue levels of PCBs to be elevated to levels orders of magnitude higher than aqueous concentrations of these chemicals.

In the U.S., the control of PCBs was mandated by Congress under the Toxic Substances Control Act (TSCA) of 1976. PCBs were the only chemicals singled out for specific attention by this law. Because of their stability, PCBs biodegrade very slowly, and they are widespread in the environment.

Since the enactment of TSCA, considerable scientific data concerning their human health effects have become available. Although the recent literature is voluminous, the information indicates that no substantial adverse human health effects have resulted from exposure to PCBs in the U.S. Some people are beginning to say that had this information been available in 1976, PCBs might not have received special treatment in the law. They point out that the hue and cry of the Yusho experience put pressure on the Congress to do something. That something is the TSCA.

But regulations issued under this law have not made the problem go away. Between 1929 and 1977, about 1.2 billion lbs of PCBs were produced in the U.S. Although U.S. chemical manufacture of PCBs has now ceased, an estimated 750 million lbs are still in use. PCBs are used in two major types of electrical equipment—in transformers that raise or lower the voltage of a power line and in capacitors, those bread-box-sized cans on utility poles that help maintain constant voltage in homes. PCBs are also present in other types of electrical equipment including electromagnets and voltage regulators in fluorescent lighting fixtures. According to one EPA estimate, there are 20 million lbs of PCBs in storage.

Over the years, careless disposal of PCBs has contaminated the surface of soil and aquatic systems in the U.S. But the situation is not unique to this country. The OECD (Organisation for Economic Cooperation and Development) in its publication *The OECD Observer* (September) noted that despite the fact that production and use of PCBs decreased dramatically in accordance with a 1973 OECD decision, disposal facilities are still needed to prevent environmental contamination by these chemicals.

The regulation trail

TSCA was passed in 1976; in 1977, the manufacture, processing, distribution, and use of PCBs (in a non-totally enclosed manner) were banned. But in May 1979, the EPA promulgated a rule establishing exceptions to the general ban. One of the 1979 exceptions permitted the use of PCBs in certain electrical equipment. EPA classified the "use" of this equipment in a "totally enclosed manner," in effect allowing this type of use to continue. Another exception established what has become known as the 50-ppm cutoff point. EPA determined that PCBs in concentrations below 50 ppm were not covered by the TSCA Section 6 (e) ban. Hence, oils and other items containing less than 50 ppm PCBs are not covered by the regulation.

Then, in 1980, in considering a suit filed by the Environmental Defense Fund, the U.S. Court of Appeals for the District of Columbia Circuit set aside these two exceptions to the ban and required the agency to look at the situation again. The court said, in essence, that the use of PCBs in some of the equipment is not in a totally enclosed manner and there is no justification for setting the 50-ppm regulatory cutoff for PCBs levels.

A first part of the EPA response to the court was due on August 1982; it dealt with the use of PCBs in electrical equipment. A second part, which was due in October 1982, partially dealt with the issue of 50 ppm. Further rule making is under way to complete

EPA's response to the remand of the 50-ppm cutoff. The 50-ppm level was stayed by the court to allow EPA time to complete its rule-making activities. Hence, EPA anticipates that the cutoff will be in effect for another two years, while EPA completes its rule making.

In response to the first part of the court order, EPA authorized the use of PCBs in certain types of electrical equipment, set forth conditions for the continued use of PCBs, and established schedules for phasing out certain PCBs transformers and capacitors. This final rule making required inspections and record keeping, among other requirements, and was immediately challenged by a host of organizations, including the Edison Electric Institute, the National Rural Electrical Cooperatives Association, the Environmental Defense Fund, the Natural Resources Defense Council, and the American Frozen Food Association. A further pronouncement from the Court of Appeals for the D.C. Circuit is imminent.

Addressing the information needs of the electric utility managers, Executive Enterprises, Inc. (New York), sponsored a meeting in Washington, D.C., at which the recent EPA regulations that are being challenged anew were discussed. The meeting on Oct. 15 addressed such questions as: What does the law say that you can or cannot do with PCBs legally? What are the problems and requirements for record keeping? What, if any, enforcement actions may the EPA be taking? In brief, there were sessions on the regulations affecting the use of PCBs, spill cleanup and reporting requirements, practical problems in complying with PCB regulations, and PCB enforcement.

Health effects meeting

An open discussion on the health effects of PCBs was initiated this May. Sponsored by the EPA, on short notice to the public, a two-day symposium for scientific information exchange on PCBs was conducted under contract with ICAIR (Cleveland, Ohio). One objective of the meeting was to review, discuss, and interpret scientific data on PCBs published since 1978 and preliminary PCB data from ongoing work. Another objective was to identify research gaps and areas of agreement and controversy. Proceedings of the May 12–13, 1982, meeting in suburban Washington, D.C. (Bethesda, Md.), entitled "Recent Advances in Exposure, Health, and Environmental Effects Studies on PCBs," are expected to be available in June 1983. Meanwhile, tapes of sessions of the symposium are available from Bowers Reporting Company (Falls Church, Va.).

Yusho, a unique experience

The Yusho (rice oil) poisoning occurred in 1968. The Yusho experience was described at an international workshop in Washington, D.C., held on March 17–19, 1980. In the proceedings of the workshop, "Plans for Clinical and Epidemiological Follow-up after Area-Wide Contamination," Robert W. Miller of the National Cancer Institute (NCI) said that the Yusho disease was first recognized because of an epidemic of chloracne that began in February 1968 on the island of Kyushu, Japan. One thousand fifty-seven people were affected; their illnesses—chloracne, headaches, nausea, and diarrhea—were quickly traced to a heat-transfer agent used during the manufacture of cooking oil. The oil contained 2000–3000 ppm PCBs, now known to be contaminated with impurities.

Some scientists and physicians in Japan and Taiwan are now saying that the Yusho effects are due to high levels of other contaminants in the rice oil, such as chlorinated dibenzofurans and quaterphenyls, which are considerably more toxic in animal tests than PCBs. The average level of total ingestion of PCBs has been estimated to be 0.5–2.0 g.

Among the 11 children born to exposed women, two were stillborn and three others were small-for-date. All showed transient symptoms such as dark cola-colored pigmentation and eye discharges. These observations indicate placental transfer of the agent. Infants who were breast-fed had higher serum PCB levels. A 13-year follow-up (1981) found PCBs in the tissues of breast-fed children, the level varying with the duration of breast-feeding. (Scientists are asking how these levels differ from the background level in the general population.) Follow-up of the affected population, thus far, has not revealed carcinogenesis or other clear evidence of adverse health effects related to this experience.

In the follow-up of some of the chloracne cases at Kyushu University there are some reports that second pregnancies, one year or more after the mothers' exposure to PCBs, seem to result in darker-than-usual (hypermelanotic) infants. Chloracne in patients first seen in 1968 persisted for two or three years.

This experience in Japan focused attention on PCBs problems elsewhere in the world. In the U.S., Holly Farms, Inc., a supplier of chickens and eggs, discovered reduced hatchability of its eggs, and traced the problem to PCBs contamination of chicken feed. No human exposure was reported in this case, which occurred in 1971. The contamination occurred in a manner similar to that of the Japanese cooking oil. PCBs, containing impurities and used as a heat-transfer fluid, leaked into the feed through pinhole erosions in the pipes.

In 1980, a second chloracne epidemic, involving 1000 persons, developed in Taiwan. Again, the source was traced to cooking oil contaminated with PCBs during manufacture. This is very similar to the Yusho experience, according to a Japanese publication on the subject.

In summary, the combination of PCBs with chlorinated dibenzofurans and quaterphenyls has caused area-wide food contamination. The chemicals may have a transplacental effect, produce chloracne, and be transmitted in breast milk.

Occupational experience

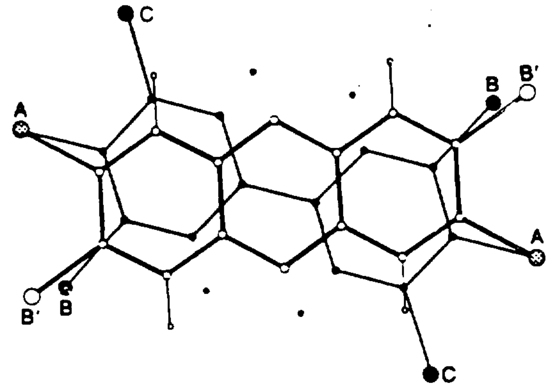
Workers in the electrical industry have been exposed to PCBs since the materials were first introduced around 1930. Aside from infrequent skin conditions which disappeared when exposure to PCBs was discontinued, no significant adverse health effects have been reported. The absence of significant health effects, even among workers with higher exposures to PCBs than Yusho patients has been explained by the absence of chlorinated dibenzofurans in the commercial mixtures.

Irving Selikoff of Mt. Sinai S[illegible] of Medicine (New York) said very extensive studies on PCBs have been done. A study of workers in the largest capacitor plants in the U.S., at Fort Edward and Hudson Falls, N.Y., was published in the *Annals of the New York Academy of Science* in 1979. Some skin effects were observed but no serious disease was reported.

In another study that has been under way for more than three years, Selikoff is investigating employee mortality in these capacitor plants. Under the direction of William J. Nicholson of Mt. Sinai, this study is jointly supported by the National Institute for Occupational Safety and Health (NIOSH), the United Electrical Workers Union, and the American Cancer Society. Selikoff indicated that a report on this study would be available in the spring of 1983.

Structural similarity of toxic compounds[a]

Overlay of planar conformation of 3,3',4,4',5,5'-hexachlorobiphenyl with TCDD[b]



[a]Toxic structures show preferred distribution polarization about the lateral chlorine atoms (A, B, and B') through resonance interactions between rings (Atoms C are also chlorine but are not in a lateral position.)

[b]TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin

Correlation of biological activity of individual PCB compounds in animals with molar polarizability

The critical rectangular distances in the molecule (3 × 10 Å) between lateral chlorine atoms appear in the most toxic structures . . .

Name of compound	Single oral dose in guinea pig LD_{50} ($\mu g/kg$)	Type of inducer of mixed-function oxidase activity in rat	Pm (molar polarizability)
2,3,7,8-tetrachlorodibenzo-p-dioxin	2	P-448	—
2,3,7,8-tetrachlorodibenzofuran	7	P-448	—
3,3',4,4',5,5'-hexachlorobiphenyl	500	P-448	106
3,3',4,4'-tetrachlorobiphenyl	< 1000	P-448	110
. . . whereas deviation from the rectangular arrangement significantly lowers the biological potency			
2,3,7-trichloro-p-dioxin	> 29 000	—	—
2,3,3',4,4',5,5'-heptachlorobiphenyl	> 3000	P-450, P-448	116
2,2',4,4',5,5'-hexachlorobiphenyl	> 10 000	P-450	157

Source: James McKinney, NIEHS

Selikoff indicated that researchers have measured the levels of PCBs in serum and in fats; currently, they are investigating dibenzofurans. This investigation is under the direction of Mary Wolff, head of the analytical chemistry unit of the environmental sciences laboratory of Mt. Sinai.

Last year, David Brown of NIOSH (Cincinnati, Ohio) reported a mortality study of 2500 PCBs-exposed electrical equipment workers from two capacitor manufacturing plants. More than 50% of these workers were exposed to PCBs on the job for more than 20 years; some were exposed for as long as 40 years. The results showed no significant excess in total mortality from cancer, cardiovascular disease, neurological manifestations, or any other cause. The overall mortality was low; overall cancer death was lower than that of the general population. If PCBs are carcinogenic, they are weak agents in humans.

In another study, Alexander Blair Smith also of NIOSH looked at workers from a capacitor plant and two electrical utility plants that loaded transformers with PCBs. His conclusion, published in 1981, was that although there were high levels of PCBs in the blood, "none of the published occupational and epidemiological studies (including our own) have shown that occupational exposure to PCBs is associated with an adverse health outcome, except for the occurrence of chloracne during the early years of its manufacture and use, and possibly during current times as well, depending on circumstances of its use and exposure."

In November 1982, NIOSH initiated a new research project to learn the reproductive history of women exposed to PCBs in the workplace. Under the direction of Michael Rosenberg, the study will look at 800 women who worked in a capacitor plant. A sample of 200 married women who worked directly with PCBs will be compared to a matched group of 200 women whose exposure was low or incidental. A questionnaire covering demographic data, occupational history, and medical history will be completed for each of the 400 workers.

Toxicological study

In August 1981, a consulting firm specializing in toxicology was charged with examining the toxicological and epidemiological literature on PCBs. The firm was to provide a professional opinion on the implication of these studies for the human health effects of PCBs. The study was performed by Drill, Friess, Hays, Loomis, and Shaffer, Inc. (DFHLS—Arlington, Va.) and was sponsored by the Electric Edison Institute and the National Electrical Manufacturers Association (NEMA). This study was undertaken in response to the previously mentioned court order.

DFHLS reported that it is not apparent how the Yusho experience—exposure by ingestion—can be related to exposure to PCBs in the U.S. workplace. Although total PCBs absorbed were similar for both groups, the dose patterns were different. The U.S. industrial worker had essentially a low-level, long-time exposure to PCBs by inhalation and skin contact. In contrast, the Yusho experience was by ingestion over a short period of time. Because of the predominant role of impurities such as chlorinated dibenzofurans in the rice oil, the study concluded that it is not possible to extrapolate acute and subchronic effects of commercial PCBs mixtures on humans from the Yusho experience.

Of the various effects noted in animal test systems, the DFHLS study found that only dermatological effects, including some chloracne and an increase in liver enzyme activity, have been clearly demonstrated in human populations at the dosage levels associated with occupational exposure. It is the firm's opinion that the risk to human health from even high level occupational exposures has been shown by the studies available to be low; therefore much lower human exposures to PCBs in the workplace and in the natural environment do not present significant human health risks.

In response

Irwin Baumel, director of the Health and Environmental Review Division of the U.S. EPA, commented on the DFHLS study. In an April 12, 1982 internal memo to Martin Halper, director of the EPA, he wrote, "... this document is very well prepared and knowledgeably written; however, it presents a review of selected reports. ... This document contends that the studies reviewed demonstrate that PCBs do not pose any serious risk of injury to human health. While we have completed only a preliminary review of this document, we do not agree that the information presented proves that PCBs do not pose any serious risks. Specifically, the areas of hepatotoxicity, mutagenesis and reproductive effects are of greatest concern and must be fully investigated."

In rebuttal to the EPA criticism, Seymour L. Friess, president of DFHLS, cautioned that "it should be emphasized that such differences in interpretation can well arise among scientists from consideration of experimental and observational studies that are not perfect or complete in every report, and that may be contradicted in other reports."

He continued, "To say that the literature on PCBs is voluminous would be an understatement of the first magnitude. DFHLS considered only those papers which, in their judgment, made a meaningful contribution to a determination of potential health effects in the human."

The view of the Chemical Manufacturers Association (CMA) is: "Any exposure to PCBs does not pose a significant health risk to humans." The CMA paper, "Summary of Health Effects of PCBs," dated November 1981, was prepared by Ecology and Environment, Inc. (Buffalo, N.Y.).

The science

Under a section in its report entitled "other health effects—enzyme induction," the DFHLS study says that the predominant effect of commercial PCBs shows up in the tests involving cytochrome containing monooxygenases, which are a family of enzymes involved in the metabolism of various toxicants.

In recent scientific research, James McKinney of the NIEHS (National Institute of Environmental Health Sciences, Research Triangle Park, N.C.) assessed the structural requirements that are important for the toxic properties of halogenated aromatic hydrocarbons. He and colleagues investigated the specific structural requirements for induction of cytochrome P-448, cytochrome P-450, and associated monooxygenase activities in rats and mice, and toxicity in the guinea pig. The guinea pig appears to be an extremely sensitive animal model for the toxic effects of these compounds. It is now quite clear that molecular geometry and electronic properties are important in eliciting biological activity of this type.

McKinney and E. McConnell in a recent publication said that studies of structural specificity for the receptor with model compounds, including several PCBs, has led them to postulate that polarizability properties are an underlying electronic basis for this activity. Measurement of this molar polarizability (Pm) for a selected number of PCBs has indeed shown a clear correlation between this property and the ability to induce cytochrome P-448, cytochrome P-450, or to be a noninducer.

All four P-448 inducers tested in this study had a Pm value of 113 ± 7, with the two mixed inducers at the high end of the range. The four strong P-450 inducers had a Pm value of 153 ± 9. The noninducer tested had a very high Pm of 211. How to calculate molar polarizability is explained in a short communication in *Chem. Biol. Interact.*, **1981**, *34*, 373–78

With the P-450 data there is no correlation between activity in rat and guinea pig toxicity data for PCBs. On the other hand, there is a correlation between P-448 activity and toxicity data in the guinea pig. McKinney says, however, "We don't know what this correlation means." He adds that there are species differences. The important question now is determining whether or not the so-called mixed inducers, (those compounds that show both P-448 and P-450 activities) are toxic.

At present, the mechanism by which P-450-inducing PCBs operates is unknown. P-448 inducers, however, are thought to interact with a specific cytoplasmic receptor, presumably a protein. Ability to bind effectively to this receptor is postulated to involve a particular spatial relationship of electronegative groups, which is dependent upon the ability to achieve a degree of coplanarity of the two phenyl rings.

With dibenzodioxins, dibenzofurans, and naphthalenes, for example, coplanarity is built into the molecular structure. In the case of PCBs, revolution around the biphenyl linkage allows the molecules to seek their lowest energy conformation. McKinney and Phirtu Singh found that for the two pure P-448 inducers, the preferred crystallographic structures are significantly nonplanar, but non-ortho substituted biphenyls have been cocrystallized in a coplanar state. As orthochlorines are added, the tendency for coplanarity decreases and is precluded by two ortho-chlorine atoms. Similarly, as ortho-chlorine atoms are added, McKinney's data indicate that enzyme induction tends to shift from P-448, to mixed or noninducing P-450.

The pure P-448 inducers, 3,3',4,4'-tetra and the 3,3',4,4',5,5'-hexachlorobiphenyls, are present in commercial mixtures in the low ppb quantities, if at all—too low to have biological significance. Therefore, the major relevance of McKinney's work on exposure to commercial PCB mixtures must be in the study of mixed-type and P-450 inducers. As shown in the table, these are considerably less toxic than the pure P-448 inducers

Prognosis

It now seems clear that new insights are being found to explain the toxicity of cytochrome P-448-inducing chemicals. More work needs to be done to understand the implication of these insights to human and environmental exposures to PCBs.

—Stanton Miller